Valentis, Inc. (formerly Progenitor, Inc., a subsidiary of Interneuron Pharmaceuticals)

Use of Gene Therapy to Treat Cardiovascular Disease

In 1994, Progenitor, Inc., received an award from the Advanced Technology Program (ATP) to develop transplantable endothelial cells from precursor stem cells, which could be genetically engineered or otherwise modified for specific medical purposes. The company believed that these endothelial-like cells could contribute to the development of new blood vessels and could be used to treat complications that often followed angioplasty. Early in their research, the company discovered that many of the endothelial cells that it was isolating expressed the Del-1 marker, an essential gene that regulates angiogenesis, the process by which new blood vessels are formed in adults. This discovery prompted the company to change its focus to this essential gene.

By the end of the project in 1998, Progenitor had developed an understanding of how the gene regulates angiogenesis and can be used to treat ischemia; it did not, however, complete the necessary research to commercialize the gene. Shortly thereafter, Progenitor went out of business, but in April 1999, Valentis, a biopharmaceutical company, acquired the rights to the specific gene and has continued to develop it for the treatment of heart disease and peripheral arterial disease. In July 2003, the company initiated Phase II of a clinical trial for the Del-1 gene.

COMPOSITE PERFORMANCE SCORE
(based on a four star rating)
* *

Research and data for Status Report 94-01-0301 were collected during March - July 2003.

Dysfunctional Endothelial Cells Thought to Lead to Vascular Disease

Endothelial cells regulate many critical physiological processes. These processes include local control of blood vessel tone, modulation of the immune response, and new blood vessel development. The malfunctioning of these cells is thought to play an important role in the onset of diseases involving blood vessels, blood flow, and arteries, such as hypertension, atherosclerosis (hardening of the arteries), and ischemia (heart attack).

In the 1990's, angioplasty (a procedure for alleviating blockage of an artery in which a balloon-tipped catheter is introduced into the artery at the point of obstruction and inflated to push the vessel open) and the replacement of vessels by grafting were the most advanced means of managing coronary heart disease; however, these procedures were limited in their effectiveness and often required follow-up procedures. Angioplasty had a relatively high incidence of restenosis, which was thought to be caused, in part, by the loss of functional endothelial cells during the procedure. Artificial devices were used to keep the blood vessels open, but the lack of efficient endothelial cell activity resulted in blood clotting or coagulation on the surface, often causing vascular obstruction and limiting the long-term usefulness of the prostheses.

Progenitor Proposes Cell Therapy Based on Endothelial Precursors

Progenitor had previously been successful in isolating cell lines with endothelial characteristics from the murine (mouse) yolk sac. It had also isolated a human yolk sac line with endothelial-like properties. The company wanted to develop the technology to use the yolk sac-derived endothelial cell lines to treat vascular disease.

The yolk sac is the first site for endothelial and blood cell development in mammals. Progenitor believed that the endothelial cell lines derived from the yolk sac might be accepted as tissue grafts more easily than other types of cell lines and could potentially contribute to the normal development of blood vessels. This would be useful in treating ischemia and restenosis following angioplasty. The cells could also reduce occurrences of restenosis by rapidly repairing the endothelial lining of blood vessels damaged by angioplasty. Cells from human yolk sacs could be obtained as by-products (i.e., exempted tissue donations) from normal full-term births.

Progenitor realized that developing this technology was a high-risk endeavor. Cellular therapy was a new field that was rapidly changing. However, if successful, Progenitor anticipated $400 million in sales in the U.S. with a potential increase to $1 billion per year if it could capture the angioplasty markets in Japan and Europe. (In 1995, there were approximately 40,000 angioplasties performed each year in Japan and 400,000 performed in Europe.) The company also believed that use of the new technology would result in an overall reduction in direct health care costs by $2 billion through more successful angioplasties and a corresponding decrease in repeat angioplasties or the alternative procedure, coronary artery bypass graft surgery, due to restenosis.

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In order to bring the concept of cell therapy based on endothelial precursors to the regulatory review stage in time to remain competitive with other emerging technologies, Progenitor needed financial assistance. After seeking funding from other sources, the company submitted a proposal to ATP and received $2 million for a three-year project.

Progenitor Anticipates Broad-Based Benefits

Progenitor believed that the successful commercialization of its technology for using yolk sac-derived endothelial cell lines to treat vascular disease would positively impact U.S. economic growth and productivity in health care delivery. As there is no cure for cardiovascular diseases, a significant amount of U.S. government funds for health care is spent on therapy for this family of diseases, particularly atherosclerosis.

Implementation of the new technology would also produce benefits to the health care industry. Commercializing the cell-based therapy would involve many different core technologies to facilitate production, distribution, and administration, including technologies for the large-scale production of cells under regulated quality practices, and technologies to characterize, store, and manipulate the cells in different applications.

Progenitor Changes Focus to Del-1 Gene

Progenitor's overall technical goal for the ATP-funded project was to isolate a human cell line with endothelial properties equivalent to the murine cell line and to find techniques to ensure that the grafted cell line would not be rejected when transplanted so that it could develop the cell line's potential for treating vascular disease, such as ischemia and restenosis.

During the ATP project, Progenitor discovered that a high percentage of the human yolk sac-derived endothelial cells that it was isolating strongly expressed the Del-1 marker, an essential gene that regulates angiogenesis. This discovery, which was made by Vanderbilt University at the time of the ATP project, had important implications because angiogenesis has therapeutic applications in several fields, including ischemia and restenosis.

At the same time, Progenitor was becoming aware of the many regulatory and safety requirements it would have to meet before commercializing a product based on its original plan. Meeting these requirements would be more time consuming and costly than the young company had anticipated. Alternatively, commercializing Del-1 products would involve meeting fewer requirements. Thus, it would cost less and involve less business risk for Progenitor. It would also result in approximately the same broad-based economic benefits as commercializing yolk sac-derived endothelial cell line products. After discussions with ATP, Progenitor decided to change its project goals and focus on developing the Del-1 marker. The company's new objectives were:

- To understand how Del-1 regulates angiogenesis
- To develop therapies to modulate Del-1 so that tumor angiogenesis could be blocked and therapeutic angiogenesis could be initiated to treat ischemia

Progenitor made considerable progress in meeting these revised goals. By the end of the ATP project, the company had accomplished the following:

- Observed that Del-1 is associated with angiogenesis in both experimental tumors and in most clinical tumors that it examined;
- Observed that Del-1 interacts with a protein that is critical to tumor growth;
- Found that Del-1 exists in several protein forms, one of which is likely to be an antagonist of Del-1's normal function (i.e., it could impede the development of new blood vessels). Progenitor thought that this could then be the basis of a cancer therapy;
- Found that the normal, full-length protein form of Del-1 is highly angiogenic and, thus, could potentially be useful for treating ischemia

Progenitor was assisted in its research by the following subcontractors: Biosupport Inc.; University of Wisconsin at Madison; University of Colorado; Ohio University; Cell Genesys; Microbiological Associates; Southern Research Institute; University of California, San Diego; Stanford University; Vanderbilt University; and, the National Jewish Cancer Center.

Valentis Continues Research of Del-1 Gene

In addition to making significant progress toward reaching its goal of developing the Del-1 marker, by the end of the ATP project in 1998, Progenitor had also published four papers, given four presentations, and filed for two patents. However, the company was also experiencing financial difficulties. A year before, Progenitor had filed an initial public offering and had purchased Mercator Genetics. As a result of the purchase, the company increased its research activities which led to a significant financial loss. By December 1998, about half a year after the ATP project concluded, the company closed.

In April 1999, Valentis, Inc., a leading company in the field of biopharmaceutical delivery, acquired the rights and intellectual property related to the Del-1 gene and continued the research initiated by Progenitor during the ATP project. By December 2000, Valentis was developing plans to conduct clinical studies with Del-1 gene medicine in patients with peripheral arterial disease (PAD) and in patients with coronary artery disease.

In 2003, Valentis completed the Phase I clinical trial of Del-1 for the treatment of PAD and initiated a Phase II clinical trial. Valentis presented the data from the Phase I clinical trial at the 6th Annual Meeting of the American Society of Gene Therapy in Washington, DC. It also published a paper entitled "Neovascularization of Ischemic Tissues by Gene Delivery of the Extracellular Matrix Protein Del-1" in the Journal of Clinical Investigations. Data for the Phase II clinical trial are expected in the third quarter of 2004.

Conclusion

With ATP's assistance, Progenitor continued its research on cell lines with endothelial characteristics, which it had successfully isolated in the past, for the treatment of heart disease. During the course of the project, however, the company observed that the Del-1 gene, which regulates angiogenesis, had a high presence in the endothelial cells that it was isolating. This was a critical discovery, as angiogenesis can be used in the treatment of ischemia and restenosis. Progenitor also realized that commercializing Del-1 products would entail meeting fewer regulatory and safety requirements. This prompted the company to change its focus to developing the Del-1 gene.

By the end of the project in 1998, Progenitor had made significant progress in understanding how Del-1 regulates angiogenesis and could be used to treat ischemia. The company, however, did not complete the research necessary to commercialize the gene. In December 1998, Progenitor went out of business due to financial difficulties. Four months later, in April 1999, Valentis acquired the rights and intellectual property related to the Del-1 gene and has continued the research initiated by Progenitor in the ATP-funded project. In 2003, the company completed a Phase I clinical trial of Del-1 for the treatment of peripheral arterial disease. It also initiated a Phase II clinical trial, which is expected to be completed in 2004.

PROJECT HIGHLIGHTS
Valentis, Inc. (formerly Progenitor, Inc., a subsidiary of Interneuron Pharmaceuticals)

Project Title: Use of Gene Therapy to Treat Cardiovascular Disease (Application of Gene Therapy to Treatment of Cardiovascular Diseases)

Project: To develop a supply of transplantable endothelial cells that might provide the basis of cell-based therapies for vascular disorders, antirejection and anticlot coatings, and "mini-organs" for in-body delivery of therapeutic agents.

Duration: 6/1/1995–5/31/1998
ATP Number: 94-01-0301

Funding (in thousands):

ATP Final Cost	$1,996	71%
Participant Final Cost	799	29%
Total	$2,795	

Accomplishments: ATP funding enabled Progenitor to conduct research on the Del-1 marker. During the project, the company gained an understanding of how the gene regulates angiogenesis and can be used to treat ischemia.

Progenitor filed for a total of 9 patents, 2 of which were granted:

- "Nucleic acid encoding developmentally-regulated endothelial cell locus-1"
  (No. 5,874,562: filed June 7, 1995, granted February 23, 1999)
- "Developmentally-regulated endothelial cell locus-1"
  (No. 5,877,281: filed June 5, 1996, granted March 2, 1999)

Commercialization Status: Since acquiring the rights to the Del-1 gene in 1999, Valentis, Inc. has continued to conduct the research on Del-1 gene medicine that was initiated by Progenitor during the ATP project. In 2003, the company completed a Phase I clinical trial and initiated a Phase II clinical trial for Del-1 angiogenesis product for the treatment of peripheral arterial disease. Valentis presented data from the Phase I clinical trial at the 6th Annual Meeting of the American Society of Gene Therapy in Washington, DC. The Phase II clinical trial is expected to be completed in 2004.

Outlook: Valentis anticipates commercializing the Del-1 gene medicine in the future for a large market.

Composite Performance Score: * *

Number of Employees: N/A

Company:
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Subcontractor:

- Biosupport Inc.
  Redmond, WA
- University of Wisconsin
  Madison, WI
- University of Colorado
  Boulder, CO
- Ohio University
  Athens, OH
- Southern Research Institute
  Menlo Park, CA
- Microbiological Associates
  Rockville, MD
- Cell Genesys
  Foster City, CA

Publications and Presentations:

Since 1995, Progenitor has published the following papers:

- Wei, Yanzhang, Thomas Quertermous, and Thomas E. Wagner. "Directed Endothelial Differentiation of Cultured Embryonic Yolk Sac Cells In Vivo Provides a Novel Cell-Based System for Gene Therapy." Stem Cells. 13:541-547. (1995).

PROJECT HIGHLIGHTS
Valentis, Inc. (formerly Progenitor, Inc., a subsidiary of Interneuron Pharmaceuticals)

- Hidai, Chiaki, Thomas Zupancic, Kalyani Penta, Adel Mikhail, Masatoshi Kawana, Elena E. Quertermous, Masafumi Fukagawa, Y. Aoka, Yasuhisa Matsui, Doros Platika, Brigid L.M. Hogan, Ralph Snodgrass, and Thomas Quertermous. "Cloning and Characterization of Developmental Endothelial Locus-1." Genes and Development. Vol. 12, No. 1, p. 21-33. (January 1998).

- Sturtz, F., L. Cioffi, S. Wittmer, M. Sonk, A. Shafer, Y. Li, N. Leeper, J. Smith-Gbur, J. Shulok, and D. Platika. "Tetracycline-Regulated Expression Vector Tightly Regulate In Vitro Gene Expression of Secreted Proteins." GENE. Vol. 221, No. 2, p. 279-285. (October 1998).

- Cioffi, L., F. Sturtz, S. Wittmer, B. Barut, J. Smith-Gbur, V. Moore, T. Zupancic, B. Gilligan, R. Auerbach, F. Gomez, F. Chauvin, M. Antczak, D. Platika, and H.R. Snodgrass. "A Novel Endothelial Cell-Based Gene Therapy Platform for the In Vivo Delivery of Apolipoprotein E." Gene Therapy. Vol. 6, No. 6, p. 1153-1159. (June 1999).

Since 1996, Progenitor has made the following presentations:

- Sturtz, F., L. Cioffi, B. Barut, S. Wittmer, J. Smith-Gbur, E. Beck, R. Snodgrass, and D. Platika. Poster. "Miniorgans: Genetically Engineered Yolk Sac Cells Secreting an Externally Regulated Gene Product." KEYSTONE Meeting on Tissue Engineering. Taos, New Mexico. (January 23-29, 1996).

- Cioffi, L., F. Sturtz, S. Wittmer, V. Moore, J. Smith-Gbur, E. Beck, T. Zupancic, B. Barut, D. Platika, and R. Snodgrass. "Gene Therapy for Atherosclerosis: Modulation of Cholesterol Levels by APOE Secreting Endothelial Cells." Joint Meeting of the ASBMB, ASIP, and AAI. (June 1996).

- Zupancic, T.J., C. Hidai, K. Penta, A. Mikhail, T. Schweitzer, V. McGaughy, J. Smith-Gbur, T. Quertermous, D. Platika, and H.R. Snodgrass. "Cloning and Characterization of Del-1, a Novel Developmentally Regulated Gene Involved in Formation of the Cardio-Vascular System." Joint Meeting of the ASBMB, ASIP, and AAI. (June 1996).

- Snodgrass, R. "Del-1 in Angiogenesis." IBC Angiogenesis Conference. (July 1997).

Since acquiring the rights to the Del- 1 gene in April 1999, Valentis has published the following paper:

- Zhong, J., B. Eliceri, D. Stupack, K. Penta, G. Sakamoto, T. Quertermous, M. Coleman, N. Boudreau, and J.A. Varner. "Neovascularization of Ischemic Tissues by Gene Delivery of the Extracellular Matrix Protein Del-1." Journal of Clinical Investigations. Vol. 112, No. 1, p. 30-41 (July 2003).

Research and data for Status Report 94-01-0301 were collected during March - July 2003.